INTRODUCTION

Pulmonary mucormycosis is a relatively uncommon and potentially fatal opportunistic fungal infection in immunocompromised hosts caused by certain fungi of the order Mucorales. Predisposing factors, in the decreasing order of frequency, are diabetes mellitus with or without ketoacidosis, organ transplantation, bone marrow aplasia, chronic obstructive pulmonary disease on low dose steroids and desferroxamine therapy for iron overload. It has also been reported in patients without any apparent immune compromise.1 Mucormycosis can present in any form; rhinocerebral, pulmonary, intestinal, disseminated and cutaneous. Pulmonary form is commonly seen in patients with hematological malignancies. Diagnosis is established by histopathologic examination of involved tissue and is more sensitive than fungal cultures. This relatively rare, but often fatal disease should be suspected in immunocompromised patients who fail to respond to antibacterial therapy. Early recognition and aggressive management are warranted to maximize cure rates. Optimum therapy requires systemic antifungal therapy, surgical resection, coupled with control of underlying disease.

CASE REPORT

A 56 years diabetic male, with uncontrolled blood sugar and neuropathy presented with distressing cough, scanty mucoid expectoration and fever for 5 days. Clinical examination was unremarkable except for crackles in left infraclavicular and mammary area. Chest x-ray revealed left perihilar infiltrate (Fig. 1). Complete blood counts were within normal limits. Sputum analysis for culture, acid fast bacilli smear and cytology yielded no diagnosis. There was evidence of mild renal failure (serum creatinine 2.1 mg%). Clinical symptoms suggested pneumonia and hence the patient was started on a course of intravenous antibiotics

Abstract

A 56 years male diabetic patient presented with recurrent left upper lobe pneumonia. Fiberoptic bronchoscopy revealed extraluminal compression of left main bronchus with an endobronchial mass obstructing the left upper lobe orifice. The lesion resembled bronchial adenoma. However histological examination revealed mucormycosis. Timely diagnosis followed by medical intervention with intravenous Amphotericin B, coupled with proper management of diabetes, ablated the tumor. Relevant literature on the subject is reviewed. ©
(Ceftriaxone 1gm IV 12 hourly and Levofloxacin 500 mg/day PO once daily for 7 days). Blood sugar was controlled with insulin. The patient responded clinically and radiologically and was discharged after a week of hospitalization.

When reviewed after two weeks, the patient had mild cough and shortness of breath. Chest x-ray showed clearance of lesion (Fig. 2). Spirometry revealed moderate obstruction with minimal reversibility. Subsequently the patient was started on inhaled steroid and ipratropium.

Two weeks later he reported to the emergency room with worsening cough, fever and breathlessness. Clinical examination revealed features of airflow limitation. Chest x-ray showed a new lesion in the left lower zone paracardiac area. Very high random blood sugar value was also noted - 652 mg%.

In view of recurrent pneumonia with uncontrolled blood sugar, further investigations were done to exclude proximal obstructive airway lesion. Computerized tomography of chest showed a mass involving left distal and lingular bronchi with consolidation of lingular segment. Patchy areas of consolidation were also noted in anterior segment of left upper lobe (Fig. 3).

Fiberoptic bronchoscopy (FOB) disclosed extraluminal compression of left main bronchus (LMB) immediately below the carina. The lumen was slit-like with total occlusion during expiration. The scope could easily be negotiated beyond this compressive segment and further ahead a smooth, lobulated, polypoidal growth was seen occluding left upper lobe orifice (Fig. 4). Biopsy specimen revealed broad, thin walled non-septate hyphae with right-angled branching on haematoxylin and eosin staining, characteristic of mucormycosis (Fig. 6).

Intravenous Amphotericin B was initiated in the dose of 50mg/day (1 mg/kg/day) and was continued for 4 weeks with close monitoring of renal parameters as well as electrolytes. Euglycemia was maintained with insulin therapy. Surgical intervention was deferred due to the proximity of the lesion to carina. Hence the patient was managed medically with close observation.

Symptoms subsided within a couple of weeks and a follow up bronchoscopy was done after 4 weeks. The ‘tumor’, which was occluding the left upper lobe, had completely vanished by then, leaving behind minimal luminal narrowing of left main bronchus (Fig. 5). One year after treatment, the patient is absolutely symptom-free. The patient is disease-free at 18 months after medical treatment.

**DISCUSSION**

Pulmonary mucormycosis is a relatively rare, life threatening, opportunistic disease caused by fungi belonging to the class Zygomycetes. The class zygomycetes is divided into two orders, Mucorales and Entomophthorales. Genera from the order Mucorales include Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Cunnighamella and Saksenaea cause an angioinvasive infection called mucormycosis. With the increasing number of immunosuppressed patients and diabetics such cases are on the increase and is no longer considered to be a rare disease. The prevalence is about 8% in autopsied patients with leukemia at post mortem and 2% in allogenic bone marrow transplant patients. Risk factors for mucormycosis are neutropenia (<500 cells/mm³), lymphopenia (<1000 cells/mm³), hyperglycemia (blood glucose level >200 mg/dl for >7 days before onset of infection), pre existing renal failure (serum creatinine >2.5 mg/dl for >14 days before onset of infection), and prolonged steroid use (>600-mg cumulative dose of prednisone in the four weeks before the onset of infection). Generally rhinocerebral mucormycosis is seen in diabetic ketoacidosis, whereas pulmonary form is often encountered in patients with haematological malignancies. Pulmonary involvement can
develop as a result of inhalation of airborne fungal spores or haematogenous spread. Pulmonary manifestations vary from a rapidly progressive fulminant pneumonia, chronic necrotizing pneumonia, slowly progressive pulmonary infection, endobronchial polypoidal lesion and intracavitary fungal ball. Most common clinical presentation is as a rapidly progressive pneumonia in those patients with underlying hematological malignancy particularly in the
neutropenic phase following chemotherapy, which is often fatal. Endobronchial polypoidal lesion is a less fulminant form of the disease and is a rare presentation which is usually seen in poorly controlled diabetic patients. It may present as a lung collapse due to obstructive lesion or a recurrent pneumonia as seen in our case. Hoarseness, a rare manifestation of endobronchial form of disease has been reported previously but the exact anatomic basis of vocal cord paralysis is not clear. Pulmonary form may also co-exist with rhinocerebral disease.

Usual symptoms by the pulmonary are nonspecific which may include fever, cough, chest pain, haemoptysis and dyspnoea which progresses rapidly. The chest radiographic findings can be diverse with no pathognomonic feature. Lobar or multilobar consolidation is the most common radiographic feature followed by solitary or multiple nodules and masses. Cavitation occurs in 26-40% of cases and air crescent sign can be seen in 5-12.5%. Pleural effusions, fistula opening to the chest wall, lung collapse due to endobronchial lesion and hilar masses are rare presentations. The disease being rare, clinical and radiographic features being nonspecific, a high index of suspicion is required for diagnosis. It is rarely suspected clinically and antemortem diagnosis is made only in 23-50% cases. Even in the present case the diagnosis was missed during initial admission. Ipsilateral recurrence of pneumonia prompted us to investigate further with bronchoscopy which unraveled the mystery.

Definite diagnosis is made by biopsy and histopathological examination of the involved tissues. Bronchoscopic biopsy itself can be catastrophic because of fatal hemorrhage. In some earlier situations cryotherapy was applied over the mass to avoid severe bleeding. This particular case, there was only minimal bleeding following biopsy. Characteristic histological feature of mucormycosis is tissue invasion by asceptate, broad (5-50 micrometer), right angled branching hyphae with a propensity to invade blood vessels. Culture is considered as gold standard for disease diagnosis and species identification. Unfortunately, the recovery of fungi in culture from involved tissue is less sensitive due to hyphal damage during processing of the specimen. It can also become nonviable during the biopsy procedure. Hence it has been agreed that microscopic identification of characteristic fungi invading affected tissues should be considered significant.

Mucormycosis has an extremely high mortality rate ranging from 25 to 80%. While pulmonary mucormycosis has a high mortality to the tune of 65%, it is 96% in those with disseminated disease. The common causes of death are fungal sepsis (42%), respiratory insufficiency (27%) and haemoptysis (13%). Massive haemoptysis may be due to vascular invasion, multiple pulmonary artery pseudoaneurysms and bronchostenosis.

The most important factors contributing to the favourable outcome are rapid diagnosis, lack of pulmonary involvement and reversal of underlying predisposing conditions immune reconstitution, systemic antifungals and urgent surgical debridement of affected tissue. Combined medical and surgical treatment is considered optimal.4-6 weeks of intravenous Amphotericin B (1-1.5 mg/kg/day) remains the mainstay medical therapy. Patients on therapy should be closely followed up for renal function and control of underlying factors. Imaging procedures and repeat bronchoscopy are desired to confirm resolution. Combined systemic antifungal therapy and topical instillation via bronchoscope have been found to be successful in certain difficult situation when systemic therapy alone failed to produce the desired results. Amphotericin B lipid complex (3-5 mg/kg/day) may be used when conventional treatment is failing or when renal toxicity develops. Azole drugs are considered ineffective against zygomycetes. But recent results in vitro suggest that some zygomycete strains (particularly absidia strains) are inhibited by relatively low concentration of itraconazole. New triazoles like voriconazole, posaconazole, avuconazole and albaconazole has emerged and are presently in different phases of clinical investigation. These drugs have a broad spectrum of activity and is effective in treating certain fungal pathogens which are resistant to existing antifungals. Recent data support the concept that high-dose liposomal amphotericin (10mg/kg/day) is the preferred monotherapy for mucormycosis. However, several novel therapeutic strategies are available. These options include combination therapy using lipid-based amphotericin with an echinocandin or with an azole (largely itraconazole or posaconazole, 200mg 4 times daily) or with all three.4 Some cases were successfully treated with Posaconazole alone, especially in post transplant diabetic patient where AmphotericinB had failed or was contraindicated due to renal failure.6 In our case, conventional Amphotericin B was used due to financial reasons.

Role of surgery in mucormycosis is not clear. Antifungal therapy is known to be inferior to combined medical and surgical therapy. The mortality in surgically treated patients was 11% which is significantly lower. Resection of involved lobe, if localized to a single lobe or surgical debridement of pulmonary lesion may provide additional benefit. Early surgical intervention can reduce the chance of fatal hemorrhage. Rigid bronchoscopic laser surgery may be done to relieve the obstruction produced by the endobronchial fungal mass. There are case reports where endobronchial lesion has also disappeared after removal with biopsy forceps without antifungal therapy. In addition to the mainstay treatment, predisposing factors such as neutropenia associated with haematological malignancy should be reversed with the use of colony stimulating factor and withdrawal of cytotoxic chemotherapy.

Medical therapy alone is rarely beneficial though there are isolated reports in the literature where either modality of treatment has been used successfully. Monotherapy with liposomal Amphotericin B has also produced a favourable response. In our case, the endobronchial tumor mass was...
successfully treated with 4 weeks course of intravenous, conventional amphotericin B alone in the dose of 1mg/kg/day (50 mg). It may be because of indolent form of the disease with less tissue necrosis and angioinvasion.

CONCLUSION

Opportunistic fungal infections like mucormycosis should be considered in the differential diagnosis of pneumonia in a diabetic patient when it fails to respond to antibiotic therapy. An early bronchoscopy is indicated in cases of recurrent pneumonia to rule out intraluminal obstructive lesion. Certain “tumors” may be medically amenable and should be diagnosed early in the course of the disease for better outcome and to prevent complications. This case is unique because of peculiar tumor-like presentation of mucormycosis which responded to medical management alone with Amphotericin B and thereby we could preserve the already compromised lung function of a patient with chronic obstructive pulmonary disease by avoiding surgical resection.

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REFERENCES